

APPROACHES TOWARDS MENSTRUAL CYCLE DISORDER THERAPY IN REPRODUCTIVE-AGED WOMEN WITH LONG COVID

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the pandemic, which involved around 540 million confirmed cases, including 6 million deaths, reported by WHO. The first known case was identified in December 2019, in China. Since then approximately 5 million Ukrainians were affected by more than 100 thousand lethal accidents [1–3].

Fever, headache and cough are prevailing symptoms of COVID-19 [5, 6]. Gastrointestinal (GI) symptoms can occur either alone or with respiratory symptoms due to the high level of angiotensin-converting enzyme 2 (ACE2) receptors in the GI tract [6–8]. The virus binds to them, shifts ACE2 activity, and affects its vital physiological functions which lead to endocrine, intracrine and local activity dysregulation both in the lung and in the gut [9]. It results in nausea, abdominal pain, and diarrhea [10].

What's more, 10–35% of respondents [11, 12], so-called long-haulers, noted prolongation of the symptoms after the recovery [13]. Long COVID includes many manifestations: from brain fog, loss of attention, confusion, nausea, general fatigue, cough, tachycardia, and palpitations to anxiety, depression, and insomnia [14].

We know that the menstrual cycle is an indicator of women's reproductive health. It is completely normal for it to vary slightly. At the same time pandemic acts as a major stressor [15] and can disturb the hypothalamic-pituitary-gonadal axis [16]. The cerebral cortex is the first part to be affected and starts the cascade of further reactions. Hypothalamus goes next and releases corticotropin-releasing hormone, which therefore induces the pituitary gland to produce and release adrenocorticotrophic hormone into the blood. Adrenocorticotrophic hormone targets are adrenal glands, which lead to cortisol [16] production, the stress hormone itself.

Objectives: to assess the efficacy of the chosen treatment approach in women with changes in premenstrual syndrome presentation and cyclicity due to long COVID with or without GI symptoms.

MATERIALS AND METHODS

A single-center, longitudinal, interventional study was held in Kyiv, Ukraine between January

and June 2021. A total of 320 women were enrolled in the study and divided equally into:

- two groups: with GI tract symptoms (n = 160, GI+) and without GI tract symptoms (n = 160, GI-);
- two subgroups: oral progesterone subgroup (n = 90) and vaginal progesterone subgroup (n = 90).

Inclusion criteria were: age between 18 and 45 years old, a signed patient informed consent, a history of SARS-CoV-2 confirmed with real-time reverse-transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swab specimen collection.

Exclusion criteria were: pregnancy, lactation, active infectious or exacerbation of the chronic disease, premenopause and menopause, or prior history of menstrual irregularities onset right before the COVID-19 positive status, and substance addiction.

GI symptoms applied to diarrhea, abdominal pain, nausea, and vomiting. Painful menstruation, mood changes, mastalgia and cycle regularity (shortest to longest cycle < 9 days by FIGO classification) were reviewed. The patients selected the symptoms that they considered to be of the greatest importance.

All groups, regardless of symptoms, received vitamin D (2000 IU orally single daily dose with a meal), valerian root extract supplements (2 tabs orally 2 times daily), and magnesium citrate (400 mg 2 tablets daily with a meal). Micronized progesterone was administered in all groups as well, but either in oral or vaginal form (200 mg orally or vaginally 2 times daily for 10 days).

Progesterone side effects, such as nausea, hypotension, compliance and vertigo were assessed.

We have examined data from the patient's records and conducted tests (blood progesterone level (Fig. 1) on the first 5 days of the cycle (normal range in follicular phase 0.2–1.4, luteal phase 3.3–28 ng/ml), ultrasound follicle scan, etc.) and surveys. Then the effectiveness of the suggested treatment was evaluated. Follow-up was performed via planned visits and by phone after 3 and 6 months.

Descriptive statistics were used to examine the responses and demographics of the participants. Continuous variables were expressed as

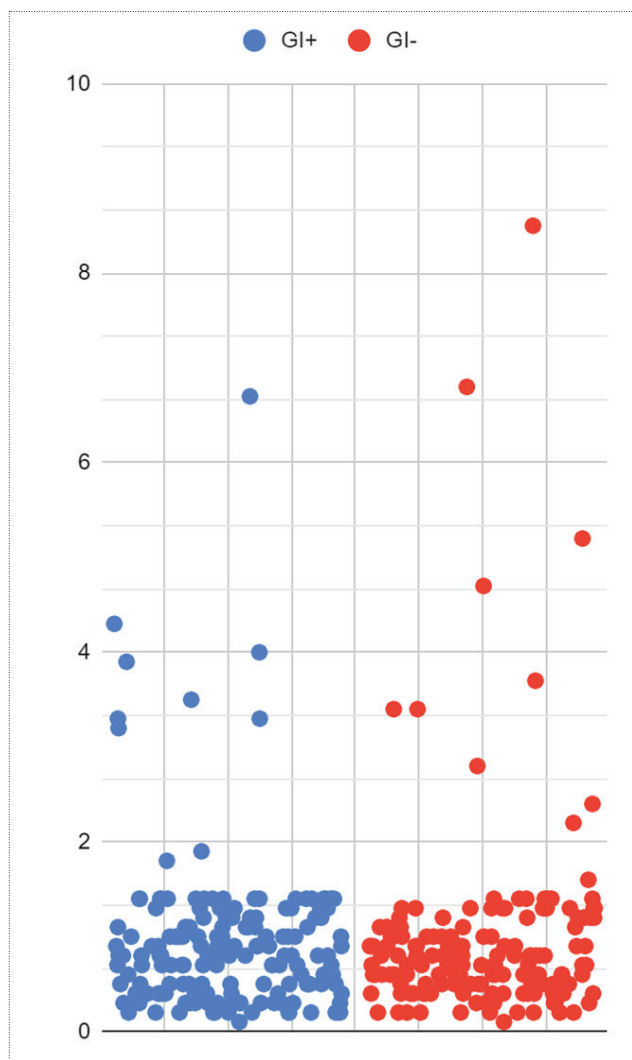


Figure 1. Progesterone level range, ng/ml

the median and interquartile range (IQR), while categorical variables were summarized as the counts and percentages in each category. Also t-tests were used for two-group comparisons. A P value < 0.05 was considered statistically significant.

The study was approved by the Ethics Committee of the P.L. Shupyk National Healthcare University of Ukraine (No. 12 from 29.11.2021). Informed contents were obtained from all patients for de-identified data use in scientific research.

RESULTS

Clinical characteristics of females with COVID-19 are shown in Table 1.

In the first group without GI symptoms on average 78% experienced relief of menstrual cycle disorders after 3 months of suggested treatment compared to 89% after 6 months. With GI symptoms on average 71% experienced improvement after 3 months, and 87% after 6 months. The vaginal progesterone [17] resulted in better results compared to oral, while on average performing 2.5–14% better. On average 6–8% experienced side effects (nausea, hypotension, less compliance) due to progesterone intake. The vaginal micronised progesterone [18] also presented better results than oral (Fig. 2, 3).

Table 1. Clinical characteristics of participants

Characteristics	Patients (n = 320)	
	With GI (n = 160)	Without GI (n = 160)
Age, years, median (IQR)	34.5 (25.00–38.00)	30 (23.75–38.25)
Race, n (%):		
European	138 (86.2)	142 (88.7)
Middle Eastern	20 (12.5)	17 (10.6)
African	2 (1.25)	1 (0.6)
BMI, median (IQR)	29.5 (23–35)	27 (23–33)
Comorbidities, n (%):		
Hypertension	38 (23.7)	34 (21.2)
Diabetes	16 (10)	16 (10)
Metabolic syndrome	38 (23.7)	32 (20)
Kidney disease	2 (1.2)	0 (0)
Cardiovascular disease	0 (0)	0 (0)
Malignancy	0 (0)	0 (0)
COVID-19 symptoms, n (%):		
Fever	108 (67.5)	112 (70)
Headache	91 (56.8)	104 (65)
Fatigue	82 (51.2)	64 (40)
Myalgia	76 (47.5)	70 (43.7)
Anosmia, ageusia	58 (36.2)	55 (34.3)
Cough	78 (48.7)	115 (71.8)
Dyspnea	35 (21.8)	44 (27.5)
GI symptoms, n (%):		
Nausea	138 (86.2)	0 (0)
Vomiting	98 (61.2)	0 (0)
Diarrhea	101 (63.1)	0 (0)
Abdominal pain	56 (35)	0 (0)
Death rate, n (%)	0 (0)	0 (0)
Treatment of COVID-19, n (%):		
NSAIDs	108 (67.5)	112 (70)
Antibiotics	96 (60)	108 (67.5)
Glucocorticoids	31 (19)	39 (24.3)
Immunoglobulins	0 (0)	0 (0)
O ₂ supplement, n (%):		
Oxygen concentrator	31 (19)	39 (24.3)
Nasal cannula	0 (0)	0 (0)

DISCUSSION

The SARS-CoV-2 pandemic was like a bolt from the blue in 2019. It has completely impacted and changed everyone's life.

Recent investigations suggest that around 56–64% [19] of convalescent women reported menstrual cycle changes since the beginning of the pandemic (menstrual volume, missed cycle, painful periods, and worsening of premenstrual symptoms). The combination of COVID-19, public health restrictions and measures, and fear all together contributed [20] to the disruption in the hypothalamic-pituitary-gonadal axis. Moreover, the long COVID itself silently affects the population's health. Talking about women, it happens in a way of disturbing reproductive health [21]. For example, with the

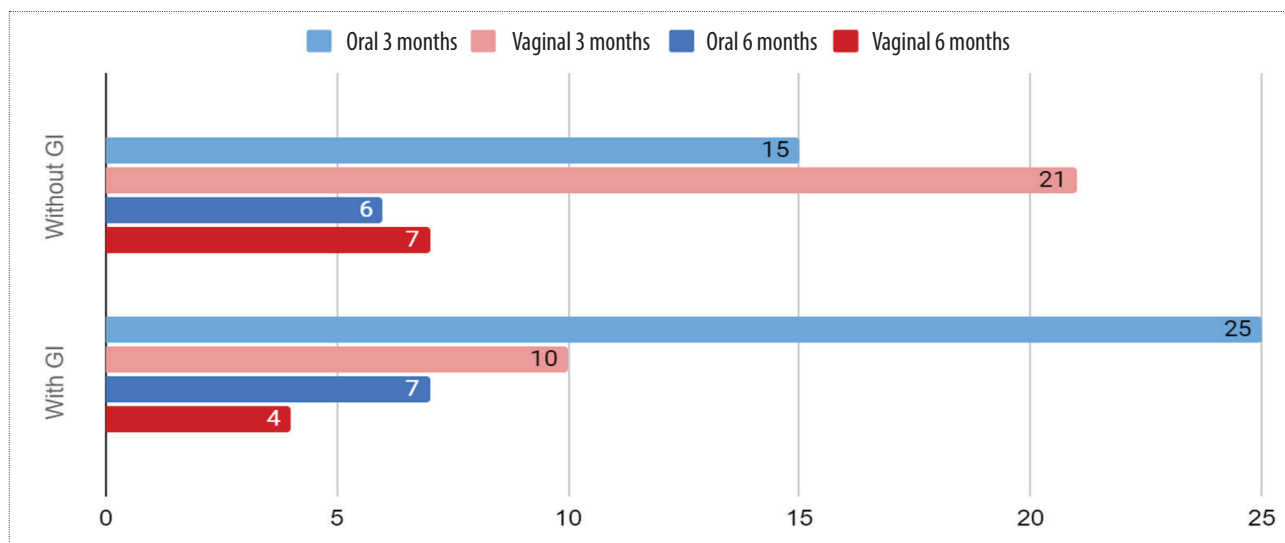


Figure 2. Side effects of progesterone intake, n

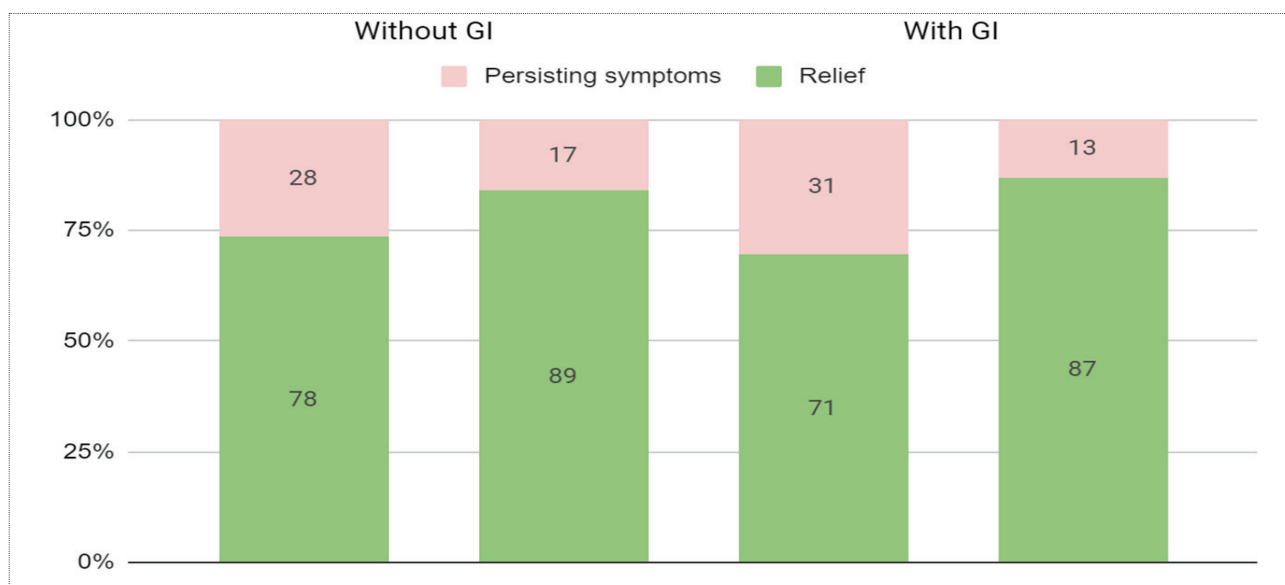


Figure 3. Symptoms relief after 3 and 6 months, %

previous SARS in 2003 outbreak, around 10% of respondents were still experiencing psychological distress [22] in a four months period.

The COVID-19 symptom pattern of the patients in our analysis represented the incidence found in other studies [4, 5]. Progesterone itself can facilitate premenstrual symptoms via modulating gamma-aminobutyric acid (GABA) type A receptors [23]. For a plethora of infected patients with GI symptoms [24], whose absorption is disrupted, the vaginal route of medicines administration may benefit, where applicable.

It is important for health care providers to understand the underlying impact of the COVID-19 pandemic on women’s reproductive health [15] and to consult patients properly [25] about the potential consequences and symptom continuation.

The study limitations are at least sample size and patient subjective self-report about the painful cycle, breast tenderness, mood swings and medications side effects.

It has now given us the urge to research global pandemics from the modern perspective while allowing us to be better prepared and armed ourselves for future pandemics which will inevitably happen.

CONCLUSIONS

The proposed approach has shown particular correction of the menstrual cycle disturbances in women with long COVID. Vaginal micronized progesterone offers more promising outcomes in patients with GI symptoms and disrupted absorption, compared to the oral variant. Further investigation is required for a more reasonable conclusion.

Conflict of interest

The authors declare that they have no competing interests.

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Background. The mirror of a female's reproductive health is the menstrual cycle. The SARS-CoV-2 pandemic itself acts as a significant stressor. This leads to women's overall health and life quality disturbance. Moreover, patients struggle with long COVID effects, which is a prolongation of symptoms after recovery. Due to the expression of angiotensin-converting enzyme type 2 receptors in the intestinal mucosa and inflammation, the gastrointestinal (GI) tract is also triggered by the virus.

Objectives. To assess the efficacy of the chosen treatment approach in women with changes in premenstrual syndrome and cyclicity due to long COVID with or without GI symptoms.

Material and methods. A single-centre longitudinal interventional study was organized. Were studied data from the conducted tests (progesterone level, ultrasound follicle scan, etc.) and surveys.

Then the effectiveness of the suggested treatment with the use of oral and vaginal forms of progesterone was evaluated. The study was held in the Kyiv City Center of Reproductive and Perinatal Medicine (Ukraine) from January to June 2021.

Results. On average 78% patients without GI symptoms experienced relief after 3 months and 89% patients after 6 months of suggested treatment. 71% patients with GI symptoms experienced improvement after 3 and 87% of them after 6 months. The vaginal progesterone had better results compared to oral form. Averagely 6–8% experienced side effects (nausea, hypotension, less compliance) due to progesterone intake. The vaginal micronised progesterone also presented better results than oral with fewer side effects compared to the total number of participants.

Conclusions. The proposed approach has shown particular correction of the menstrual cycle disturbances in women with long COVID. Vaginal micronized progesterone offers more promising outcomes in patients with GI symptoms and disrupted absorption, compared to the oral form.

Further investigation is required for a more reasonable conclusion.

Keywords: long COVID, reproductive health, premenstrual syndrome, gastrointestinal tract.

ПІДХОДИ ДО ТЕРАПІЇ ПОРУШЕНЬ МЕНСТРУАЛЬНОГО ЦИКЛУ В ЖІНОК РЕПРОДУКТИВНОГО ВІКУ З ТРИВАЛОЮ КОРОНАВІРУСНОЮ ІНФЕКЦІЄЮ

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Обговорювання. Менструальний цикл є індикатором репродуктивного здоров'я жінки. Пандемія SARS-CoV-2 діє як серйозний стресовий чинник і може легко вплинути на загальне здоров'я та якість життя жінок. Крім того, пацієнтки борються з тривалими наслідками COVID-19, тобто пролонгацією симптомів після одужання. Шлунково-кишковий тракт (ШКТ) також є мішенню для вірусу через високу експресію рецепторів ангіотензинперетворювального ферменту типу 2 і запалення слизової оболонки кишечника.

Мета дослідження: оцінити ефективність запропонованих методів лікування в жінок зі зміною циклічності та появою передменструального синдрому внаслідок тривалого перебігу коронавірусної інфекції з симптомами з боку ШКТ або без них.

Матеріали та методи. Було організовано одноцентрове поздовжнє інтервенційне дослідження. Вивчено дані, отримані в результаті проведених досліджень (рівень прогестерону, показники фолікулометрії та ін.) і опитувань. Потім оцінювали ефективність запропонованого лікування із застосуванням пероральної та вагінальної форм прогестерону. Дослідження проводили на базі КНП «Київський міський центр репродуктивної та перинатальної медицини» (Україна) з січня до червня 2021 року.

Результати. У середньому 78% жінок без симптомів з боку ШКТ відчували полегшення після 3 місяців та 89% — після 6 місяців запропонованого лікування. Результати пацієнток зі скаргами з боку ШКТ: 71% відчували покращення за 3 місяці, 87% — за 6 місяців. Вагінальна форма прогестерону показала кращі результати порівняно з пероральною. У середньому 6–8% опитуваних повідомили про побічні ефекти (нудота, артеріальна гіпотензія, зниження compliance) через застосування прогестерону. Вагінальний мікронізований прогестерон також показав кращі результати проти пероральної форми і мав меншу кількість побічних ефектів порівняно з небажаними явищами в загальній кількості учасниць.

Висновки. Запропоноване лікування сприяло певному зменшенню порушень менструального циклу та проявів передменструального синдрому в жінок із тривалою коронавірусною інфекцією. Крім того, через шлунково-кишкові симптоми та порушення всмоктування вагінальний мікронізований прогестерон продемонстрував кращі результати щодо ефективності лікування порівняно з пероральною формою.

Для більш детального вивчення питання потрібно продовжувати дослідження.

Ключові слова: тривала коронавірусна інфекція, репродуктивне здоров'я, передменструальний синдром, шлунково-кишковий тракт.